

REMARKS

Claims 1-30 are pending in the application. With entry of the present Response, claims 1 and 30 are currently amended. Claims 31-33 are new, and no claims are cancelled.

Amendments to the Claims

Claim 1 has been amended by insertion of a semicolon behind the first occurrence of “space” on line 5. It is respectfully submitted that insertion of an ‘and’ in this location is inappropriate as the ‘and’ should be located before the final feature of the claim, in this case the first synthetic polymer.

The phrase “...within the confinement structure, wherein the first synthetic polymer is trapped in the confinement structure, to prevent peeling of the first synthetic polymer from the substrate” has been replaced with “...wherein the confinement structure is filled with the first synthetic polymer such that the first synthetic polymer lies against an inner wall of the confinement structure, the first synthetic polymer being immobilized by the confinement structure to prevent peeling of the first synthetic polymer from the substrate”.

The feature that the confinement structure is filled with the first synthetic polymer finds its basis on page 13 line 26 – page 15 line 20 of the application as filed where it is apparent that the pot formed by the confinement structure (see page 4 lines 29-32 of the application as filed) is filled with the first synthetic polymer, such that it is clear from the application as filed that the first synthetic polymer lies against an inner wall of the confinement structure.

The feature that the polymer is immobilized by the inner wall of the confinement structure to prevent peeling of the first synthetic polymer from the substrate can be derived from page 15 lines 22-28 of the application as filed, where it has been disclosed that the first synthetic polymer is trapped inside the confinement structure. The meaning of the term ‘trapped’ becomes unequivocally apparent in the next part of this sentence, where it is stated that the MIP may also be immobilized on the substrate surface, thereby clearly showing that ‘trapping’ means immobilization.

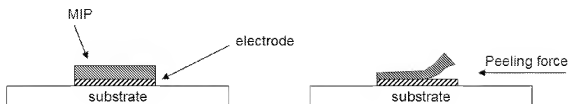
Claim 30 has been amended in a similar manner, i.e. by replacing "...within the confinement structure, wherein the molecularly imprinted polymer is trapped in the confinement structure, to prevent peeling of the molecularly imprinted polymer from the substrate" with "...wherein the confinement structure is filled with the molecularly imprinted polymer such that the molecularly imprinted polymer lies against an inner wall of the confinement structure, the molecularly imprinted polymer being immobilized by the confinement structure to prevent peeling of the first synthetic polymer from the substrate".

Dependent claims 31-33 are new. Support for claim 31 may be found on page 16, lines 20-27, and page 17, lines 5-14. Support for claims 32 and 33 may be found on page 13, lines 4-11 and 26-30; and Figures 5 and 7 plus accompanying descriptions therein.

It is noted that the amendments made to claims 1-30 make it clear that the synthetic polymer extends over the substrate surface of the first inner volume, as this volume is bound by the confinement structure, and it has now been clarified that the first synthetic polymer lies against the inner wall of the confinement structure, which is a clear structural feature. Also, it should be appreciated that the feature that the first synthetic polymer is immobilized by the confinement structure is a clear structural feature as it must imply physical interaction between the edges of the first synthetic polymer and the inner wall of the confinement structure.

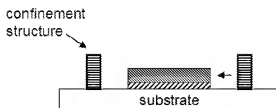
Rejection (1) under 35 U.S.C. § 103(a)

Claims 1-12, 14, 16, 17 and 20-25 stand rejected under 35 U.S.C. 103(a) as being anticipated by Gumbrecht in view of Blanco-López. On page 8 of the Office Action, the examiner recognizes that "For sensing application, MIPs can be immobilized on electrode surface for electrochemical detection" (emphasis added by the applicant).



As identified in the application as filed (page 3 lines 13-21) and demonstrated in the image above, such sensors suffer from a limitation in their lifetime due to peeling (delamination) of the MIP from the sensor electrode. This is because a laterally directed shear force, which for instance may be applied by a sample streaming in a lateral direction over the electrode surface, causes the MIP to eventually release from the electrode surface. In other words, it has been realized by the present inventors that such sensors suffer from the problem that when applied on an electrode surface, the MIP is in fact not at all properly immobilized but in fact suffers from this unwanted peeling. This problem has not been previously recognized.

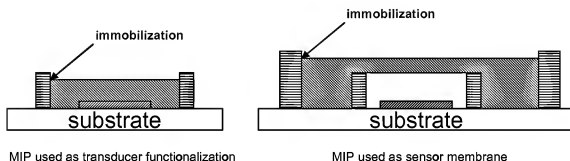
The skilled person, when combining the teachings of Gumbrecht and Blanco-Lopez, would arrive at an arrangement as shown below:



As Blanco-Lopez teaches that a MIP is patterned onto the sensor electrode area and immobilized thereon, the skilled person would apply the MIP to the transducer on a surface of the inner space delimited by the confinement structure. However, as indicated by the horizontal arrow inside the inner space, the electrode/MIP interface in such an arrangement is still prone to being subjected to a shear force, such that the eventual peeling of the MIP cannot be prevented. Hence, it is respectfully submitted that the assertion of the examiner that "MIPs immobilized on the sensing surface of Gumbrecht would inherently/intrinsically prevent peeling of the first synthetic polymer (MIPs) from the substrate" is in fact technically incorrect.

As already stated in the response to the previous office action, if a skilled person were to apply the silanisation and sandwich deposition techniques taught by Blanco-López, indeed only the transducer surface would be covered by the polymer. As such, it would still be susceptible to peeling as the edges of the polymer are not protected by the confinement structure, as explained above. Similarly, the photografting technique taught by Blanco-López yields a polymer that only covers the transducer surface, such that it would still be susceptible to peeling as the edges of the polymer are not protected (immobilized) by the confinement structure.

In contrast, the present invention as defined in claim 1 provides a solution to overcome this problem:



Because the first synthetic polymer is used to fill the confinement structure, the polymer lies against an inner wall of the confinement structure such that it is immobilized by the confinement structure, such that peeling can no longer occur, as the electrode/polymer or substrate/polymer interface is protected from being exposed to the shear force. This is a structural difference over the prior art to achieve a functional result that cannot be achieved by a combination of the prior art.

As shown above, the filling of the inner volume does not have to be complete (i.e. up to the edge of the confinement structure); it merely requires that the first synthetic polymer (MIP) is in contact with the inner wall for the immobilization to become effective.

The example drawing above shows two different confinement structures, one with a single limiting structure (left hand pane) and one with two limiting structures (right hand pane). It should be noted that the above drawing is a simplified schematic drawing

that depicts selected non-limiting examples for the sake of explaining the principle of the invention only. It should be clear from the application as filed that the confinement structure may have multiple limiting structures defining different inner spaces, with one of the inner spaces filled with the first synthetic polymer.

It should be understood that the crucial insight of the present invention is that the vertical edge of the polymer should be protected from exposure, which is achieved by lying the polymer against the inner wall of the confinement structure. It should, however, also be understood that it is not necessary to completely fill the confinement structure with the first synthetic polymer as the fill level has no impact on the protection against peeling as long as it is ensured that the edge of the first synthetic polymer lies against this inner wall.

It is reiterated that there is nothing in either Gumbrecht or Blanco Lopez that would provide the skilled person with an incentive to deviate from the common practice of applying a MIP to an electrode surface only. More specifically, there is nothing in Gumbrecht that teaches that the confinement structure can be used as an immobilization anchor for a polymer in its inner space, nor does Gumbrecht suggest that such immobilization would have any beneficial effect.

Hence, the applicant submit that it would not be obvious for the person of ordinary skill in the art to adjust the combined teachings of Gumbrecht and Blanco-López and cover both transducer and substrate by filling the confinement structure with the first synthetic polymer and immobilizing it on the confinement structure as the skilled person would have no expectation of reasonable chance of successfully solving the issue of polymer peeling.

For the sake of completeness, the applicant further notes the following. In response to the applicant's previous argument that no deposition techniques are available to the skilled person to form a first synthetic polymer inside a confinement structure, the examiner has asserted that "photografting can be used as an immobilization means for coating the substrate of Gumbrecht with the MIPs of Blanco-López.

This, however, is respectfully disputed. Blanco-López in Table 5 clearly teaches photografting onto a transducer surface only. There is no hint that this may be extended

to the surrounding substrate, nor is there any hint that such extension may have some benefit. It is in fact highly unlikely that this would work anyway as photografting essentially comprises a chemical reaction between the monomer and the underlying surface, and not every surface is suitable for such photografting techniques. There is no evidence that the MIP could be photografted onto a substrate.

The examiner further appears to suggest on page 17 that “the prior art does not teach that such immobilization techniques would be susceptible to peeling of the MIPs from substrate surfaces” is evidence of “MIPs immobilized on the sensing surface of Gumbrecht would inherently/intrinsically prevent peeling of the first synthetic polymer (MIP) from the substrate”.

This is strongly refuted. The fact that a prior art reference does not mention a problem of course does not mean that the problem does not exist. The applicant submits that the prior art simply has failed to recognize that such peeling problems exist. The present inventors instead have come to this valuable insight (i.e. have recognized the existence of this problem) and have found this problem unexpectedly may be solved as claimed, i.e. that the confinement structure of Gumbrecht can fulfill the previously unknown function of immobilization of a polymer.

For at least these reasons, applicants respectfully submit that Claims 1-12, 14, 16, 17 and 20-25 would not have been obvious in light of the cited references.

Rejection (2) under 35 U.S.C. § 103(a)

Claims 13, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gumbrecht in view of Blanco-López, and in further view of Leyland-Jones (U.S. Patent Publication No. 2003/0053950).

The deficiencies of combining the teachings of Gumbrecht with Blanco-López are detailed above, and the applicants have submitted that claims 1 and 25 are nonobvious and allowable. Since claims 13, 28 and 29 derive their allowability from the independent claims 1 and 25, and because the rejection of these claims relies on the improper combination of Gumbrecht with Blanco-López, the applicants submit that, for at least

these reasons, claims 13, 28 and 29 would not have been obvious in light of the cited references.

In addition, the applicant respectfully points out the following. The examiner has intimated that Leyland-Jones teaches a method of characterizing multi-determinant metabolic phenotypes by detecting metabolites of metabolic pathways in a biological sample in order to provide individualized treatment.

However, propofol is not a metabolite as stated in the examiner's report. Instead propofol is being metabolized by CYP2E1 to other substances. Hence the teaching of Leyland-Jones are not applicable to the claims limited to propofol. Since the action of propofol is derived from the drug itself and not from the metabolite, detection of the metabolite does not really provide a direct means of optimizing the delivery of propofol to the patient. Propofol is rapidly distributed into various compartments in the body. It therefore exists in a number of compartments and is rapidly interchanged between them. Measuring the metabolite only does not assist the medical practitioner in predicting this complex situation. Instead, measuring the drug concentration **itself** (rather than its metabolite) enables the medical practitioner to assess the effect of the drug and optimize treatment.

Rejection (3) under 35 U.S.C. § 103(a)

The examiner has rejected pending claims 15 and 30 as being obvious over Gumbrecht in view of Blanco-López and in further view of Ulbricht. The deficiencies in basing an obviousness rejection on Gumbrecht in view of Blanco-López are discussed above. There is nothing in Ulbricht to cure these deficiencies.

It is respectfully submitted that Ulbricht does not teach the use of a sensor comprised of a reference material within an additional confinement structure on said sensor, as required by claim 15. Instead, Ulbricht teaches the use of a reference sample for the purpose of demonstrating that the imprinted membranes actually work, as is apparent from Example 5: "The significantly higher values for the peroxidase TTP surface as compared to the very weak signal of the non-imprinted reference sample show the stronger adhesion of horseradish peroxidase to the synthetical receptor structures under saturation of the sorption capacity in the examined concentration range". The

applicant is at a loss why this would provide the skilled person with an incentive to provide a sensor comprising at least one additional confinement structure having a non-imprinted reference material therein, in addition to a confinement structure including the first synthetic polymer, for the simple reason that when providing such a sensor suitable for industrial applicability, there should no longer be any question marks over whether or not the MIP actually works. As such, there is no need to provide a reference for the purpose taught by Ulbricht.

Moreover, even if a skilled person were able to apply the teachings of the cited prior art in further view of Ulbricht, as alleged by the Examiner, he or she would not arrive at the claimed invention. In other words, because claim 15 depends from claim 1, as amended (via claim 11) and because the combined teachings of Gumbrecht, Blanco-López and Ulbricht fail to arrive at claim 1, the mere fact that Ulbricht discloses a reference material does not suffice to encompass claim 15 inclusive of all its limitations.

For at least this reason, applicants respectfully submit that claim 15 would not have been obvious in light of the cited references.

It is reiterated that Ulbricht does not teach the benefit of an “in-sensor” reference material that can be used to calibrate the binding to a MIP exposed to the same sample. See specification, page 18, lines 25-26. In other words, Ulbricht is silent about the possibility of using the reference material sensor to improve the accuracy of the MIP sensor, as is for instance clearly stated in claim 30.

For at least this reason, applicants respectfully submit that claim 30 would not have been obvious in light of the cited references.

Rejection (4) under 35 U.S.C. § 103(a)

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gumbrecht in view of Blanco-López, as applied to claim 1, and in further view of Dickert et al. (U.S. Patent No. 6,223,589).

The deficiencies of combining the teachings of Gumbrecht with Blanco-López are detailed above, and the applicants have submitted that claim 1 is nonobvious and allowable. Since claims 18 and 19 derive their allowability from claim 1 as amended,

and because the rejection of these claims relies on the improper combination of Gumbrecht with Blanco-López, the applicants submit that, for at least this reason, claims 18 and 19 would not have been obvious in light of the cited references.

Rejection (5) under 35 U.S.C. § 103(a)

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gumbrecht in view of Blanco-López, as applied to claims 1 and 25, and in further view of Dieffenbach et al. (U.S. Patent No. 5,089,421).

The deficiencies of combining the teachings of Gumbrecht with Blanco-López are detailed above, and the applicants have submitted that claims 1 and 25 are nonobvious and allowable. Since claim 26 derives its allowability from claim 1 as amended, and because the rejection of this claim relies on the improper combination of Gumbrecht with Blanco-López, the applicants submit that, for at least this reason, claim 26 would not have been obvious in light of the cited references.

CONCLUSION

Applicants believe that no extension to time is required for submission of this response. In the event that an extension is needed, this conditional petition of extension is hereby submitted. Applicants request that deposit account number 19-4972 be charged for any fees that may be required for the timely consideration of this application.

It is submitted that all of the pending claims are now in a condition for allowance, and Applicants respectfully request reconsideration of the application and issuance of a notice of allowance. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

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Respectfully submitted,

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